Clinical Review

Pregnancy and Inflammatory Bowel Disease

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Conclusions about the relationship between the pathophysiology and treatment of inflammatory bowel disease and the physiology and management of pregnancy are based on the results of several large physician surveys and retrospective chart reviews. Patients with active disease fare worse than those with inactive disease. There is little evidence that pregnancy affects the course of inflammatory bowel disease or that inactive inflammatory bowel disease affects the course of pregnancy. Judicious medical therapy is effective in controlling inflammatory bowel disease during pregnancy. Sulfasalazine or steroid therapy should not be withdrawn in a patient who needs it to achieve or maintain a quiescent state of inflammatory bowel disease during the course of pregnancy. Immunosuppressive therapy should be avoided. Aggressive medical therapy with total parenteral nutrition in a team approach with a gastroenterologist, surgeon, and perinatologist usually avoids the need for surgical intervention during pregnancy with a good fetal outcome in a patient whose disease is active. Contraception against pregnancy need only be considered in those patients whose disease is so severe that operative therapy is imminent.

(Zeldis JB: Pregnancy and inflammatory bowel disease. West J Med 1989 Aug; 151:168-171)

Issues relating to fertility and pregnancy are a major concern of patients with inflammatory bowel disease (IBD). A more optimistic appraisal about the relationship between pregnancy and IBD than was first thought is the result of the earlier diagnosis of IBD, a greater awareness by physicians of the nutritional needs of their patients, advances in prenatal care and fetal monitoring, progress in radiologic techniques, and an increased understanding of the natural history of the disease. Much can be concluded based on the experience of several large retrospective series and surveys. In this review I discuss the current thinking about many of the issues around fertility, pregnancy, and inflammatory bowel disease.

Inflammatory Bowel Disease and Fertility

Recent studies have shown that ulcerative colitis does not affect fertility.[1-3] Other studies that found reduced fertility were probably flawed owing to short follow-up periods, patient selection, and an inadequate medical control of the disease[4,5] or inadequate numbers of patients observed.[6]

The effect of Crohn's disease on fertility is controversial. Earlier investigations found that fertility was reduced.[7,8] These studies did not take into account the birth control practices of women who followed the advice of their physicians that IBD adversely affects pregnancy and that pregnancy could exacerbate IBD. A study of 40 women with Crohn's disease has suggested that women might have been "subfertile" and that they became fertile after the surgical resection of their involved viscera.[8] The authors did not discuss whether fertility in these women correlated with their nutritional status before and after their operations. In general, studies have failed to consider whether severe perineal problems affect fertility. A small percentage of women with Crohn's disease will have fistulization to fallopian tubes or tubo-ovarian abscesses that render them permanently sterile.

Khosla and co-workers found that the infertility rate of 112 married women with Crohn's disease was similar to that in the general population.[9] The results of a case-control study of 275 women with Crohn's disease from five European countries are in sharp contrast to those of Khosla and associates.[10] Mayberry and Weterman determined whether the patients were using birth control, were having sexual relations, and were advised by their physicians not to become pregnant. Patients with Crohn's disease had a notable reduction in the number of children born and a substantial increase in the incidence of prematurity. The rate of miscarriage and cesarean section was unaffected by Crohn's disease. The site of the disease did not affect these findings. Although 40 women with Crohn's disease were told not to have children, the women used birth control less but still had fewer pregnancies.

Sulfasalazine treatment causes oligospermia, reduced sperm motility, and an increased proportion of abnormal morphologic features of sperm. This is manifested as decreased fertility. Withdrawing sulfasalazine reverses these defects to normal, and patients presumably return to pretreatment fertile states.[11-14] The consequences of long-term sulfasalazine therapy on male fertility remain to be fully assessed.

In contrast to the results of total colectomies in men for cancer, proctocolectomy for ulcerative colitis rarely results in permanent impotence (1.5% in a series of 130 patients), temporary impotence, or retrograde ejaculation.[15] In rare cases, women will have postoperative dyspareunia that results from unintentional lacerations of the vagina during the

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ABBREVIATIONS USED IN TEXT
IBD = inflammatory bowel disease
TPN = total parenteral nutrition

removal of the rectum. Proctocolectomies in women appear to have a negligible effect on fertility.

Effects of Inflammatory Bowel Disease on Pregnancy

Ulcerative Colitis

Ulcerative colitis does not influence fetal outcome except in severe cases that necessitate surgical intervention. In these, the risk of fetal wastage is high.[16,17] Total parenteral nutrition (TPN) and better fetal monitoring may be improving the prognosis for this group of patients with severe colitis.[17,18] The incidence of spontaneous abortions, stillbirths, prematurity, low-birth-weight infants, and fetal malformations is not increased over the general population. In a recent report, a higher percentage of low-birth-weight infants was found compared with the normal population.[6] This finding, based on the results of only 12 infants, is contrary to that of another recent report of 136 infants of mothers with ulcerative colitis where the incidence of low birth weights was normal (5.4%).[19]

Crohn's Disease

The risk of spontaneous abortion, prematurity, and low-birth-weight infants in patients with Crohn's disease is related to the activity of disease at the time of conception.[7-9] The site of involvement does not appear to affect pregnancy. Surgical intervention for Crohn's disease has resulted in a high degree of fetal wastage.[8] The nutritional support given these women with severe disease was not specified. Recently, normal deliveries in women with severe exacerbations of IBD were the result of long-term maintenance on total parenteral nutrition until delivery.[20-25] A few patients receiving home TPN for their Crohn's disease conceived, maintained, and nursed while on a regimen of TPN.[26,27] One pregnancy managed this way resulted in a child with a partial cleft palate. Whether this was a complication of the therapy or coincidental is not certain.

Effects of Pregnancy on Inflammatory Bowel Disease

Ulcerative Colitis

Pregnancy has not been shown to affect the course of ulcerative colitis. In one recent study involving 97 women with ulcerative colitis,[19] the spontaneous risk of an exacerbation of bowel disease per patient per year in nonpregnant women of child-bearing age was determined to be 32%. When pregnant, the same women's risk rose insignificantly to 34%. Exacerbations of the disease occurred most often in the first and second trimester. In this same series, the three colectomies that were done had no effect on the course of the pregnancy or delivery. Patients who have active disease at the time of conception tend to continue to have the same intensity or an exacerbation of their colitis throughout their pregnancy.[28] Therapeutic abortion has not affected the course of ulcerative colitis in these patients. Thus, although pregnancy is not contraindicated in patients with ulcerative colitis, it is probably best to recommend to patients that they become pregnant when their disease is in a quiescent state. Despite what was initially thought, there is no evidence that an initial attack of colitis during pregnancy is any more severe than that found in nonpregnant patients. Furthermore, the activity of the disease in one pregnancy is probably independent of that which will be experienced during a subsequent pregnancy. Usually flexible sigmoidoscopy provides a relatively safe means to assess the activity of disease in pregnant patients with ulcerative colitis.

Crohn's Disease

Pregnancy does not increase the risk for an exacerbation of Crohn's disease. Nielsen and colleagues found a 44% risk of exacerbation per patient in 59 women who were not pregnant but a 38% risk in the same women when pregnant or after delivery.[23] Patients whose disease was inactive at the time of conception had about a 60% chance of its remaining inactive during the course of their pregnancy. Most patients (more than 50%) who had active disease at the time of conception had either no change or worsening of their disease. While many clinicians have thought that a fairly high percentage of patients will have increased activity of their disease in the postpartum period, Nielsen and co-workers found that postpartum relapses are usually mild and easily managed medically.[23] Mogadam and colleagues found that 23% of 145 women with Crohn's disease had decreased disease activity in the postpartum period, 62% had no change, and 15% had an exacerbation.[28]

Pregnancy and Ileostomy

The investigations into the effect of an ileostomy on pregnancy have mainly involved patients who have had total proctocolectomies for ulcerative colitis and not Crohn's disease. The theoretic possibility exists that the presence of an ileostomy might increase the likelihood of fallopian tube obstruction, lead to dyspareunia, or create psychological difficulties that could interfere with sexual relations. Despite these concerns, ileostomies have not been shown to affect fertility or the course of pregnancy.[19,29,30] Usually pregnancy has little effect on ileostomy function, although the change in shape of the abdomen may require a new appliance.[31] The fluid and electrolyte balance may be more difficult to manage in a nauseated patient with an ileostomy. In one study, 10% of patients with ileostomies had an intestinal obstruction during pregnancy.[30] Increased abdominal pressure may occasionally cause a stomal ileal prolapse. This usually occurs in patients who have had an ileostomy placed less than a year before becoming pregnant.

Similarly, successful term pregnancies have been reported with women who had had a total colectomy with an ileal pouch-anal anastomosis.[32,33] Three of six patients had a transient deterioration of anorectal function during their third trimesters that resolved after delivery.[33]

Medical Therapy for IBD During Pregnancy

Steroids

Corticosteroid administration in pregnant women only rarely results in fetal pituitary adrenal suppression and other fetal complications.[34] This may be due to the placental metabolism of cortisol to the less active cortisone. The concentration of prednisone and prednisolone in a fetus is eight times less than that in the mother. Steroid therapy in pregnant women does not increase the risk of cleft palate as it does in mice. Most studies of the effects of corticosteroid therapy on

pregnancy were done in patients who had diseases other than IBD. Reinisch and associates found a higher percentage of newborns with low birth weights born to mothers who had received 10 mg per day of prednisone during the entire course of their pregnancy compared with a matched control group.[35] Mogadam and co-workers surveyed patients who had IBD and received various drug therapies.[36,37] The use of steroids was found to have no effect on the fetal outcome compared with the general population. Thus, although steroid therapy is not contraindicated during the course of pregnancy and should be used to help control IBD, it should be kept in mind that there is a suggestion in the literature that steroid therapy may cause an increased risk of having a low-birth-weight infant. While adrenal suppression is not common, it should be looked for in infants of mothers who received corticosteroids.

No firm conclusions can yet be made about the effects of steroids on the ability to conceive, on the fetus when administered before conception, and on spermatogenesis.[22] Prednisone and prednisolone pass poorly into milk, and the amount of steroid ingested by a nursing infant is negligible.

Sulfasalazine

Sulfasalazine therapy for IBD during pregnancy has not been associated with fetal wastage, congenital abnormalities, neonatal jaundice, or kernicterus despite various theoretic conjectures based on human experience with other sulfonamides.[38] At birth, the neonatal serum concentration of sulfasalazine is comparable to that in the mother. The elimination of the drug by neonates is slower than by adults.[39] A negligible amount of sulfasalazine is found in the milk of lactating women taking therapeutic amounts of the drug, but the concentration of sulfapyridine, the major sulfa metabolite of sulfasalazine, is 45% that in maternal serum.[1,39] Neither sulfasalazine nor sulfapyridine displace bilirubin from its albumin binding sites, and, therefore, their use does not increase the incidence of neonatal jaundice or kernicterus in neonates.[40] As with steroid therapy, sulfasalazine therapy should be continued throughout pregnancy and after delivery if medically indicated to control IBD. A favorable outcome of pregnancy appears to depend on keeping IBD in remission and thus takes precedence over theoretic considerations about the effects of steroid and sulfasalazine therapy on the fetus. The effects of sulfasalazine use on male fertility have been alluded to earlier.

Mercaptopurine, Azathioprine, and Metronidazole

Mercaptopurine and azathioprine should not be administered during pregnancy as their safety is not yet established. Animal models have shown that these immunosuppressives may cause severe disorders in fetuses including lymphopenia, thymic hypoplasia, immunoglobulin deficiency, low cortisol levels, and chromosomal abnormalities. Patients with IBD who are taking these drugs should be weaned from them before becoming pregnant. Some clinicians have recommended a therapeutic abortion for patients who become pregnant while receiving these drugs,[22] based on an uncertainty about the effects on human fetuses. More than 1,000 renal transplant recipients have had successful pregnancies despite immunosuppressive therapy.[41] Of 103 births in women with renal transplants who were taking azathioprine, 7 infants had birth defects. The mothers taking higher doses of azathioprine had a higher incidence of infants with these anomalies.[42] The time interval between discontinuing the drug and becoming pregnant required to reduce the drugs' toxic effects is not known. Terminating the pregnancy based on the mother's previous and concurrent use of azathioprine and mercaptopurine must therefore be considered elective and not mandatory.

Metronidazole is mutagenic to bacteria on the Ames assay and at high doses is tumorigenic to rats, but the drug has not been teratogenic to other animals or humans. Because of the concern about theoretic teratogenicity, manufacturers recommend that the drug not be used during the first trimester of pregnancy. Metronidazole can therefore be used to control IBD in the second and third trimesters of pregnancy, if it is clinically indicated.[43]

Conclusion

For the most part, inflammatory bowel disease and pregnancy appear to be independent processes. Because the nutritional needs of patients increase during pregnancy and during flares of the disease, astute nutritional management is essential for a successful outcome of pregnancy. Pregnant patients with active disease fare worse than those with inactive disease. There is little evidence that pregnancy affects the course of IBD. Conversely, ulcerative colitis does not affect pregnancy except in severe cases, and some studies suggest that Crohn's disease in mothers may predispose the neonates to low birth weights. Sulfasalazine and steroid regimens are effective in controlling IBD during pregnancy and should not be withdrawn in a pregnant patient who requires them to maintain or achieve a quiescent state of disease. Immunosuppressive therapy should be avoided, but the use of such drugs is not an absolute indication for terminating a pregnancy. A team approach to pregnancy in a woman with inflammatory bowel disease with a gastroenterologist, surgeon, and perinatologist has increased the likelihood of a successful outcome. A woman of child-bearing age with IBD should not be discouraged from becoming pregnant if her disease is quiescent or mild. Contraception may have a place if the disease is moderate to severe and the likelihood of surgical intervention is imminent.

The most succinct and well-written summary of IBD and pregnancy for both physicians and patients is a pamphlet, "Questions and Answers About Pregnancy in Ileitis and Colitis," distributed free by the National Foundation for Ileitis and Colitis, 295 Madison Avenue, New York, NY 10017 (telephone 212-685-3440). Other medical reviews of this subject are by Vender and Spiro,[22] Warsof,[44] Sorokin and Levine,[45] Korelitz,[46] Fielding,[47] Donaldson,[48] Hanan and Kirsner,[49] and Miller.[50]

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